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(54) SPRAYABLE GERMICIDAL FOAM COMPOSITIONS

(71) We, MUNDIPHARMA A.G., a Swiss Corporation organised under the laws of Switzerland, of Alban-Vorstadt 94, Postfach, 4006 Basel, Switzerland do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to novel sprayable germicidal compositions which may be applied as a foam directly to an injured tissue surface to provide a durable semi-permeable germicidal protective barrier to skin and mucous membranes in a manner which is essentially pain-free. A particularly desirable feature of the new compositions is that they may be adapted for convenient dispensing from pressurized containers so that the formed germicidal foam may be applied directly to a wounded, abraded, burned or injured tissue surface with minimum tissue manipulation and tissue injury.

In particular, the present invention relates to sprayable compositions comprising silver sulfadiazine, silver sulfathiazine, silver sulfaphenazole; an antibiotic compound or a salt thereof an iodophor substance including povidone-iodine or a complex of elemental iodine with a detergent as active germicidal agent; a silicone compound, for example, dimethylpolysiloxane; a nonionic surface active agent; a fatty alcohol; a fatty acid and an aqueous glycol solvent to provide a stable foam matrix, the whole being packaged in pressurized container with gas aerosol propellant.

When the germicidal composition is applied to the injured tissue surface, the resultant foam possesses especially desirable long-lasting and durable properties of a kind which were previously unobtainable with pressurized foams known in the art. The lasting, durable properties of the foam formed, together with its uniform micropore character, provide a desirable semi-permeable germicidal barrier to wounded tissue surfaces to inhibit infection and at the same time to avoid tissue maceration by allowing vapour interchange. Furthermore, the excruciating pain which is ordinarily encountered when germicidal preparations, as are presently used, are applied to the skin of the patient in the treatment and prevention of infection of burned, wounded, or injured skin, is now eliminated when the new sprayable germicide-containing compositions are used.

Skin which has been burned, abraded, wounded or otherwise injured is extremely vulnerable to infection so that it becomes necessary to provide a germicidal barrier to avoid infection which, in the presence of extensive tissue injury, may result in death. It has been recognized that infection is one of the major factors to complicate the treatment in the severely burned patient, and the therapeutic need to degerm burned, wounded or abraded skin is essential to recovery.

The entire range of microbicidal agents have been used to degerm injured skin and mucous membranes. While it is generally acknowledged that iodine is perhaps the best germicidal agent, in view of its broad microbicidal spectrum, and that the newer organic iodine derivatives known as iodophors, provide a substantial benefit in reducing the noxious, toxic properties of iodine, there are still many inherent limitations on the use of elemental iodine products in the treatment of the seriously burned patient and the patient with severely abraded, wounded skin and mucous membranes.

The attempt to utilize the metal salts of the sulfa drugs also failed because of the inherent allergic reactions known for this class of antiseptic medications, when these are used topically, and also because of the added toxic effects of the silver ion when the silver salts of the sulfa drugs, such as silver sulfadiazine are used. These agents not only do not relieve patient

morbidity but they also increase the number of toxic reactions and serious side effects reported for these agents. The silver salts of the sulfa drugs such as silver sulfadiazene and silver sulfaphenazole also present the further limitation to their use, in the well known reaction between silver ions and halide ions such as are found in all physiological exudates. These chemical reactions not only destroy the ionic balance of the injured tissue surface but also poison the tissue cell by the combination of the cellular proteins with the silver ion. Similarly, the salts of the antibiotics provide either an acid pH or an alkaline pH which lead to inherent problems of pain and tissue irritation, as well as variable drug activity because of neutralizing properties exerted by physiological fluid.

Another problem limiting the degerming of injured skin arises from the nature of the pharmaceutical compositions used to carry the germicidal active ingredient and the methods for their use. A common method of obtaining a topical degerming action is to apply an antiseptic ointment, or solution, to the injured surface, of such thickness as to provide a germicidal barrier over the entire wounded area. However, the mechanical spreading of such germicidal ointments and/or solutions causes such severe pain that in many instances the administration of anaesthetics and narcotics is required. Since the application of the presently utilized germicidal agents must be repeated many times during the day, and because these compositions lack sustaining power and are subject to being washed away by physiological exudates, the noxious effects caused by the pain and consequent analgesic, anaesthetic and narcotic medications pose a serious threat to the patient's life, as well as greatly to increase morbidity.

A further limitation inherent in the compositions used to degerm severely injured, burned or abraded skin surfaces is their inability to provide for vapour exchange in order to avoid maceration of the wounded skin surface. Thus, the spreading of a thick ointment over the injured area may effectively exclude air-borne contaminants but it also prevents the exchange of essential gases and moisture vapour necessary for the healing process. Moreover, the exclusion of air provides anaerobic pockets which serve as incubators for foci of infection. When solutions are applied to the skin, these are rapidly washed away by the tissue exudates and transudates.

In view of the inherent limitations known for microbicidal compositions presently used to degerm burned, wounded or injured skin, the ideal antimicrobicide composition to be used for the purpose should possess the following properties:

(a) Be essentially pain-free upon application to the injured tissue even when repeated, multiple therapeutic procedures are required each day.

(b) Provide an effective germicidal barrier which would permit an exchange of the moisture and gases thereby avoiding tissue maceration.

(c) That the germicidal compositions have a sustained, lasting capacity when applied to abraded and/or burned skin and not be washed away by tissue exudates.

(d) That the germicidal compositions be conveniently and easily applied to the injured skin surface.

(e) That the germicidal compositions be pharmaceutically stable, have reproducible and homogenous characteristics and be microbicidally effective.

(f) That the germicidal compositions be safe for use on humans and animals.

Sprayable compositions have been proposed in the art as a means of overcoming certain of the limitations of the compositions and methods used to degerm burned, injured and abraded tissues, but the formulations proposed for such use as a topical spray have failed to achieve their desired goals and in fact have added new problems. Thus for example, the pain of application of the spray compositions was not eliminated and spray formulations to degerm injured skin contain local anaesthetics. Such compositions are described, for example in U.S. Patent No. 2,782,975 and U.S. Patent No. 2,801,201.

Both solutions and ointments have been utilized as sprayable compositions but these failed to overcome the problem of porosity for gaseous interchange and also gave rise to pockets which acted to incubate microorganism. Furthermore, when hydrophilic compositions, either as an ointment or a solution, were utilized these were rapidly washed away and did not provide any lasting adherent to the injured skin surface. When hydrophobic compositions were utilized, as for example, mineral oil preparations, they coated the wet abraded skin surface unevenly and again resulted in pockets which served as foci of infection by incubating microorganisms. Thus, the object of providing an essentially pain-free germicidal barrier which possesses sustained lasting adherent capacity still remains to be achieved with the prior art sprayable compositions.

This invention therefore provides a sprayable pharmaceutical composition for topical application to the injured skin of humans and animals comprising,

a) an aliphatic fatty alcohol of the formula ROH, in which R represents a saturated or unsaturated alkyl group of from 10 to 18 carbon atoms, or a mixture thereof.

b) an aliphatic fatty acid, of the formula RCOOH in which R represents a saturated or

unsaturated alkyl group of 14 to 18 carbon atoms, or a mixture thereof, the concentration of the fatty acid being from 1 to 3 parts by weight of fatty acid for each part by weight of fatty alcohol.

c) a nonionic surface tension reducing agent which is poly (oxyethylene)-poly(oxypropylene)-polyethylene polyol compound; an octylphenoxypoly-(ethylenoxy)-ethanol compound or a fatty acid polyoxy-alkyl ester of a hexahydric alcohol or a mixture being at least equal to one-half of the combined weight of the fatty alcohol and fatty acid moieties but not greater than three times the weight of the fatty alcohol present.

d) an aqueous aliphatic glycol mixture the glycol being a polyoxyethylene glycol having a molecular weight of 200 to 800; propylene glycol, glycerine or a mixture thereof, in critical proportion of from 0.5 to 2.0 parts by weight of aliphatic glycol, to 7.5 parts to 30 parts by weight of water.

c) a therapeutically sufficient quantity of a microbicidally active agent, a suitable liquid aerosol propellant which is propane, isobutane, dichlorodifluoromethane, dichlorofluoromethane, chlorofluoromethane, 1,1,2 trichloro- 1,2,2 trifluoroethane, dichlorotetrafluoroethane, carbon dioxide, nitrogen or a mixture thereof; in sufficient quantity to provide a ratio of from 0.5 parts to 3 parts by weight of said propellant to 7. to 9.5 parts by weight of sprayable composition,

the whole being packaged on the pressurized container, filter with a release value, to permit the release of the formed foam for application to the injured skin. The application to injured skin results in a durable foam which provides a safe and effective, pain-free, germicidal barrier to burned, abraded or wounded skin and mucous membranes. Upon release of the pressure, the composition is delivered from the container to the burned, abraded or injured skin or mucous membrane surface in the form of a foam which possesses desirable lasting qualities, and a uniform and reproducible micropore matrix which permits a gaseous exchange while providing an effective germicidal barrier to the tissue surface. The active germicidal agents is fully available from the topical foam to the injured tissue and the release rate of active ingredient is such as to avoid a rapid flooding of the area. The foam retains its structure on the exposed tissue surface for periods up to nine hours after application.

It has further unexpectedly been found that the addition of from 0.1 parts by weight to 5 parts by weight of a pharmaceutically acceptable silicone compound, for example, dimethylpolysiloxane, dimethylsiloxane or methyl-siloxane, to the above described composition prevents the coalescence of the micropore matrix, with the consequent modification in foam properties, when pH active germicides are used. Thus, agents capable of shifting the hydrogen ion potential of the composition, which in turn affect the properties of the formed foam will require the silicone stabilizer to prevent foam-coalescence and thereby reduce vapour exchange on the moist skin.

The invention also provides a method for preparing a sprayable pharmaceutical composition for tropical application to the injured skin of humans and animals comprising the steps of:

a) mixing from 0.5 to 1.5 parts by weight of the aliphatic glycol with from 7.5 to 30 parts by weight of water,

b) adding a nonionic surface tension reducing agent in a concentration at least equal to the combined weight of fatty alcohol and fatty acid moieties set forth in step c below,

c) melting one part by weight of the fatty alcohol and from two to three parts by weight of the fatty acid,

d) mixing the molten fatty alcohol-fatty acid mixture of step c with the aqueous-glycol solution obtained as a result of step b and stirring until a homogeneous dispersion results,

e) adding a therapeutically sufficient quantity of the germicidal agent, and stirring until homogeneous dispersion results,

f) adding one part of the pharmaceutically acceptable liquid aerosol propellant to each nine parts of dispersion obtained as a result of step e and packing into a suitable pressurized container fitted with a release valve.

This method preferably further comprises the addition of a suitable pharmaceutically acceptable buffer to maintain the pH of the concentrate at between pH4 and pH6.

The ease of application of the foam avoids tissue irritation and pain. However, it is important to recognize that the pain-free characteristics of the sprayable compositions described herein are not due to its being a foam or to the ease of its application since side-by-side comparison testing of the present germicidal foams with those known in the art reveals that other foam formulations utilizing the same active ingredients do cause pain upon application to injured skin, in contrast to the present sprayable compositions. The preparations described herein are stable and homogenous with reproducible physical and pharmaceutical properties and are safe and effective for use in degerming the tissue of humans and animals.

Examples of particularly suitable aliphatic fatty alcohols include cetyl alcohol and stearyl

alcohol, and examples of particularly suitable aliphatic fatty acids include stearic acid and palmitic acid.

In order to achieve effective degerming, it is preferred to use a broad spectrum antimicrobial agent. While it is generally recognized that elemental iodine is perhaps the most effective germicidal agent, its corrosive, tissue irritating properties have restricted its usage to degerm wounded tissue. However, the newer iodine derivatives, such as iodophor compounds, have eliminated many of the noxious limitations of elemental iodine, while retaining its desirable broad spectrum antimicrobial properties.

The preferred iodophor compound of the class of iodophor compounds remains its first discovered member, povidoneiodine, which is marketed under the tradc namc of BETADINE (Tradc Mark) and has been extensively scientifically studied since its inclusion in U.S. Patent No. 2,739,922. It is important to recognize that the class of organic iodophor compounds consists of two essentially different types of iodine derivatives; those formed as a loose mixture complex of elemental iodine with a surface active detergent, and the non-detergent organic iodine compound. Povidone-iodine is the only known non-detergent iodophor compound which has been established to be safe and effective for use in humans and animals, and consists of the complex compound formed from elemental iodine and povidone. The other organic chemical members of the general class of iodophor compounds consist of a loosely-bound complex of iodine with a detergent surface active agent, for example, such surface-active detergents as nonylphenoxypoly(ethyleneoxy)-ethanol; polyoxypropylenepolyoxyethanol; sodium N-coco-N methyltaurate; coconut oil-fatty amides and undecoylium chloride, to form the corresponding iodine iodophor complexes. When a member of the class of iodophor germicidal agents described above is desired for use as the active degerming agent then the concentration of the particular iodophor compound selected is preferably from 1 to 15 percent by weight of the weight of the composition.

Antibiotic substances may also be utilized as a degerming active ingredient in the present composition and the entire range of antibiotic compounds as is used in topical anti-infective therapy may bc included in the new compositions. Examples of the separate classes of antibiotics which are useful as germicidal active ingredients in the present compositions include:

(a) Aminoglycosides which contain one or more aminosugars, such as glucosamine or neosamine, and are linked by glucoside linkages to a basic 6-membered carbon ring, as for example, streptidine or sterphine. Examples of such antibiotics are gentamycin, kanamycin sulfate, streptomycin sulfate and other salts, neomycin sulfate and neomycin undecylenate.

(b) The cephalosporins, characterized by the cephalosporanic acid moiety include such agents as cephalexin, cephaloglycin, cephaloridines, cephalothin sodium cefazolin sodium and cephapirin sodium.

(c) The macrolides are a special group of antibiotic compounds containing a macrocylic lactone moiety containing 12 or more carbon atoms in the primary ring. Macrolides useful as active germicidal agents in the present compositions include such agents as erthromycin, nystatin, rifampin, amphotericin-B, mitasamycin, oleandomycin, spromycin, proleandomycin and their salts and mixtures of the same.

(d) Penicillin antibiotics which are natural products obtained by culturing Pencillium species, and include synthetic antibiotic compounds which are 6-α-carboxyamine derivatives, include such agents as ampicillin, penicillin G and its salt, carbenicillin disodium, dicloxacillin sodium, methicillin sodium, nafcillin sodium, oxacillin sodium and phenethicillin potassium.

(e) The tetracycline antibiotics include tetracycline and its salts, chlortetracycline hydrochloride, demeclycline and its acid, salts, doxycycline and its salts, methacycline hydrochloride, minacycline hydrochloride, oxytetracycline and its salts.

(f) Miscellaneous antibiotic substances include bacitracin and its metal salts, colistin, capreomycin sulfate, gramicidin, and Polymyxin B sulfate.

The concentration range for the antibiotic substances used in the compositions of the invention will vary with the particular compound, and preferably ranges from 0.1% by weight to 15% by weight, based on the weight of the composition. The exact concentration of the selected antiobiotic agent to be incorporated in the composition will vary with the patient's needs, as well as the germicidal potency and sensitivity of the organisms being treated.

Those members of the class of p-aminobenzene sulfonamide derivatives which are known as sulfa drugs and are useful in dermatological therapy have a special use in the degerming burned skin. In particular such sulfa drugs as silver sulfacetamide, silver sulfadiazine, silver sulfaphenazole, and sulfamylon are preferred compounds of this class to be incorporated in the present compositions. When the sulfa drugs are used to degerm the skin, the preferred concentration in the composition is between 0.5 and 5% of the weight of the composition.

Other antimicrobial agents useful to provide a degerming action in the present compositions include silver nitrate, silver proteinate, the nitrofurane compounds, hexachlorophene,

gentian violet and the quaternary ammonium germicides which includes alkylbenzydimethyl amino salts.

When the germicidal compositions are used to disinfect, treat or degerm wounded, abraded or burned skin, these are applied topically as a formed foam which involves a three-phase system.

(a) The foam matrix which comprises a hydrogen-bounded complex of an aliphatic fatty alcohol of the formula ROH in which R is an unsaturated and/or saturated hydrocarbon chain consisting of from 10 to 18 carbon atoms in chain length, hydrogen-bonded with a saturated and/or unsaturated aliphatic fatty acid of the formula R.COOH in which R is from 14 to 18 carbon atoms in chain length;

(b) a solution and/or suspension of therapeutically active ingredient in a specially formulated aqueous solution having a dielectric constant at strength to support the formed hydrogen-bond between the fatty alcohol and the fatty acid, and

(c) an immiscible liquid aerosol propellant preferably having an interfacial tension of less than 2 dynes/cm^2 at the interface of the liquid aqueous solvent.

It is necessary to recognize the interrelationship of the separate phases to the unexpected new and novel properties of the new hydrogen-bonded foams, which distinguish these compositions from the foam compositions of the prior art. The hydrogen-bonded foam matrix provides a micellular structure to the formed foam which engulfs the liquid germicidal composition, at the same time providing a rigidity to the foam. Water, a strongly polar solvent, has the desirable dielectric constant to form a hydrogen-bonded complex through a solvation reaction but also has certain inherent physical-chemical limitations for use in foam formulations. It therefore becomes necessary to formulate the aqueous solvent to overcome the physical limitations of water at the same time as the dielectric constant of the solvent is preserved at a strength to support the formation of a hydrogen-bonded complex through a solvation reaction. The preferred interfacial tension limit of less than 2 dynes/cm^2 between the immiscible liquid aerosol propellant and the germicidal composition, helps to form a uniform micropore character to the foam, preferably so that the micelle porosity is less than 40 microns in diameter, and thereby provide for optimal release of active ingredient to the skin surface and enable the exchange of gaseous vapours to prevent maceration of the covered tissues.

It has unexpectedly been found that, when the amounts of the components making up the separate phases were altered so that these amounts exceeded the quantities set forth in the claims, the formed foam did not have the desirable properties of the new foam compositions. Furthermore, when the ratio of the separate phases to each other was altered from those specified in the claims, the formed foam did not have the desirable physical properties determined for the new foams and also did not release the active ingredient at the desired rate. It is the special characteristics of the novel three-phase foam composition that distinguish the subject foams from those of the prior art.

It is known that polar solvents are made up of strong dipolar molecules, have marked hydrogen-bonding properties and react with dissociated chemical compounds. The interreaction between a solvent and a dissociable chemical compound is termed solvation and involves the orientation of the solvent molecules about the formed ions and/or charged particles of the solute. Such orientation however, only occurs when the dipoles of the solvent are directed to, and complexed with, the charged particles or ions of the solute through hydrogen-bonding. A polar solvent that enters into and forms a solvated hydrogen-bonded complex must possess the ability to keep the solvate-charged particles apart with minimum energy expenditure and this property is reflected in the dielectric constant for the solvent.

Chemicals having a strong tendency to dissociate and form hydrogen-bonded complexes are not so readily fragmented or dissociated by strong polar solvents as are compounds having a lesser tendency to form hydrogen bonds. It is recognized that water is a strongly polar solvent with a dielectric constant of 78.5, a molar dipolarization of 17.4 and dipole moment of 1.85, and therefore enters into solvation reactions to form strong hydrogen-bonded complexes. While water has highly desirable electrical properties as a polar solvent for general use in foams, its use as a solvent wherein a hydrogen-bonded matrix is formed between two hydrophobic moieties, as for example a fatty alcohol and fatty acid, presents certain problems since complex formation would be interfered with by the strong solvation reaction characteristic of water. Moreover, its use in formulations of medicated foams has several other inherent limitations which make it necessary to modify the properties of water as a solvent in a foam formulation.

The high vapour pressure, volatility and high evaporation index of water provide a foam of limited durability. When such aqueous foams are exposed to the atmosphere, any solvation-reaction, hydrogen-bonded complex which may be formed are destroyed and the foam rapidly collapses. This foam matrix collapse would result in the formation of a water and vapour resistant barrier over denuded skin which would not permit the interchange of gases

and vapour.

Since the continuous external phase of the foam matrix is hydrophobic, then the release of active ingredient contained in the enclosed aqueous fluid solvent is impeded and therapeutic efficacy is hindered. The overall volatility and high vapour pressure of the aqueous solvent, together with the solvated collapse of the foam matrix, cause rapid drying after topical application of the foam, together with less-than-satisfactory release of the active ingredient.

It has unexpectedly been found that, when a critical quantity of a semi-polar, non-volatile, humectant solvent is added to the strongly polar solvent, water, that there is a modification in the overall di-electric properties of the solvent-mixture which results in a reduced di-electric constant for the solvent-mixture, which does not destroy the hydrogen-bonded formed foam matrix through solvation. This reduced di-electric constant for the solvent-mixture now supports the hydrogen-bonding of the formed foam matrix to stabilize the complex formed between the fatty-alcohol - fatty-acid which results in new and unexpected lasting properties of the foam; an increase in gas and vapour exchange of the foam, as well as highly desirable release of the active ingredient from the foam to the skin and mucous membrane surface. Since the process of dissociation is a basic step in the hydrogen-bonding process and involves separation of cations and anions followed by an orientation of the molecules of the solvent about the charged ions, the di-electric strength and type of polarity of the solvent becomes the important determinant to its capacity to support a formed covalent hydrogen bond. As electrical solvation forces of the solvent decrease, the more lasting becomes the formed complex between a hydrophobic fatty alcohol and a hydrophobic fatty acid, which constitute the foam matrix.

Propylene glycol, glycerine and a polyoxyethylene glycol compound having a molecular weight of from 200 to 800, are utilized as semi-polar solvents to modify the electrical properties of the polar water solvent. These semi-polar solvents, i.e. propylene glycol, glycerine and polyoxyethyleneglycol, are strong dipolar molecules, but they do not enter into solvation reactions to form solvated hydrogen bonds and thereby decrease the solvation capacity of a mixed solvent. The modification of the strongly polar electrical properties of water by propylene glycol, glycerine and the polyoxyethyleneglycol not only contribute materially to the strength of the fatty alcohol-fatty acid formed matrix, but also convey humectant, nonvolatile properties to maintain a polar-semi-polar fluid balance which controls overall foam stability, gas and vapour interchange as well as the release of active ingredient, all of which are reflected in the improved highly desirable therapeutic activity of these foams.

It has further unexpectedly been found that the proportion of fatty acid to fatty alcohol was critical to the formation of the hydrogen-bonded complex of the foam matrix and that the proportion of this formed complex to the volume of polar solvent was also critical, as was the proportion of semi-polar solvent to polar solvent in establishing a desirable electrical balance for the solvent. The critical ratio of fatty alcohol to fatty acid was found to be one part fatty alcohol to two parts fatty acid, with a preferred range being from 0.5 to 1.5 parts by weight of fatty alcohol to 1.0 to 3.0 parts by weight of fatty acid. The critical ratio of the semi-polar solvent to polar solvent was found to be 1:15 with a range of from 0.5 to 2.0 parts by volume of semi-polar solvent for each 7.5 parts to 30 parts by volume of water, as the strongly polar solvent. The optimum ratio of the combined fatty acid - fatty alcohol component to semi-polar solvent is 1:27 with a preferred range in such ratio of from 1.5 to 4.5 parts by weight of combined fatty alcohol - fatty acid component to 45.0 parts by weight of solvent.

When the above described compositions are mixed with one part of a suitable aerosol gas propellant for each nine parts of composition and the whole packaged in a pressurized container fitted with a release valve, a highly desirable germicidal foam is formed when the pressure is released. This foam possesses superior lasting properties and is capable of providing a desirable germicidal topical coating to skin and mucous membranes. It is necessary to achieve uniform dispersion or solution of the aerosol gas propellant in the fluid composition to produce a uniform porosity within the formed foam, in order to permit satisfactory gaseous interchange while providing a germicidal barrier. It was found that when a nonionic surface tension reducing agent is present in the preferred concentration of from 1 to 3 parts by weight, said amount being at least equal to one-half the combined weight of the fatty alcohol - fatty acid matrix, there was a lowering of the interfacial tension between the fluid germicidal concentrate and the gas propellant, to less than 2 dynes/cm^2 thereby causing uniform microporosity in the formed foam.

A nonionic surface tension reducing agent or mixture of nonionic surface tension reducing agents may be used to reduce the interfacial tension between the liquified propellant phase and the fluid phase to provide a uniform distribution of phases and to result in a fine micropore character in the formed foam and such nonionic surface tension reducing agents may be advantageously used:

The nonionic surface tension reducing agents are

(a) the poly(oxyethylene)-poly(oxypropylene)-polyethylene polyol compounds, known in the trade as Pluronic (Registered Trade Mark) Polyols, which are marketed by the BASF Wyandotte Corporation and are described in U.S. Patent No. 2,674,619;

(b) the octylphenoxypoly-(ethylenoxy)-ethanol compounds, known in the trade as Igepal CA compounds which are marketed by GAF Corporation, New York City and

(c) the fatty acid-polyoxyalkyl esters of hexahydric alcohols, known in the trade as Spans (Registered Trade Mark) and Tweens (Registered Trade Mark) which are described in the Carolina Journal of Pharmacy, Vol. 33, p. 465, (1952) and the Merck Index, 8th Edition, p. 973.

Furthermore, the lowered surface tension of the aqueous phase and the reduced interfacial tension to below 2 dynes/cm^2, between the liquid propellant and fluid phase, serves to provide a uniform distribution of the liquified gas propellant within fluid lipophilic and hydrophilic phases to result in a uniform micropore character in the formed foam. This micropore foam serves to enhance the release of germicidal agent and exchange of gaseous vapours, which materially enhance the germicidal activity and utility of the formed foam barrier.

Any pharmaceutically acceptable liquifiable gas aerosol propellant suitable to prepare pharmaceutical foams may be used as the propellant for the present compositions. Liquid acrosol propellants such as fluorinated hydrocarbons, fluorochlorinated hydrocarbons, hydrocarbons and inert gases are the preferred propellants. The halogenated hydrocarbons are primarily derived from methane, ethane and cyclobutane and are prepared by replacing one or more of the hydrogen atoms of these compounds with one or more chlorine and/or fluorine atoms. The fluorinated and/or chlorinated hydrocarbons are non-polar compounds that are miscible with non-polar solvents and, in general, these agents are not miscible with water.

The preferred halogenated hydrocarbon propellants include trichlorofluoromethane, with a boiling point of about 24°C.; dichlorodifluoromethane, with a boiling point of about -30°C.; dichlorofluoromethane, with a boiling point of about 9°C.; chlorodifluoromethane, with a boiling point of about 48°C., and dichlorotetrafluoroethane, with a boiling point of about 4°C. Mixtures of halogenated hydrocarbon propellants may also be used and a mixture of trichlorofluoromethane and dichlorodifluoromethane is particularly useful.

Hydrocarbon propellants are also useful in forming germicidal foams but their flammability limits their general use. However, mixing with a fluoronated and/or chlorinated hydrocarbon and/or the inert gases such as carbon dioxide and nitrogen makes it possible to reduce the flammability hazard. Hydrocarbon propellants have several special advantageous properties which are desirable to the present three-phase aerosol foam system in that they have a unique chemical stability, do not react with halogens and possess a better solubility characteristic than the other liquified gas propellants.

When the selected aerosol propellant is used, the ratio of gas propellant to composition is one part gas propellant and nine parts of the composition and the whole is packaged in a suitable pressurized container fitted with a suitable release valve. When the container pressure is released, the formed foam extrudes as a highly desirable composition to provide a germicidal cover to protect and degerm burned, injured and/or abraded skin and mucous membranes. The foam formed has an average pore size of less than 20 microns in diameter with a range of from 5 to 40 microns in pore diameter. After one hour open exposure, the foam height is 100% of its initial value with a calculated half-life of about 5-7 hours. There is no phase separation after four hours of closed exposure at room temperature.

A preferred composition providing effective germicidal foam cover to wounded, burned and/or abraded skin is prepared by placing 75 parts by weight of purified water in a suitable container, fitted with a stirrer and warming device, and adding 5 parts by weight of propylene glycol; 0.3 parts by weight of nonylphenoxypolyethyleneoxyethanol and 1.7 parts by weight of poly(oxyethylene)-poly(oxypropylene)-polyethylenepolyol, which is known in the trade as Pluronic F-68, and the whole warmed, under constant stirring until a clear solution is obtained.

In a separate vessel, 1 part by weight of cetyl alcohol is mixed with 2 parts by weight of stearic acid and the whole melted. The melt of the cetyl alcohol-stearic acid mixture is added with vigorous stirring to the warmed aqueous-propylene glycol solution, which was earlier prepared and maintained at the same temperature. The pH of the composition is adjusted to be not less than pH 4 and not greater than pH 6 and the heat source removed. As the composition cools, 10 parts by weight of povidone-iodine is added and the composition stirred until complete solution is achieved. The pH of the solution is adjusted to be not less than pH 4.8 and not greater than pH 6.0. The finished composition is a thick, amber-coloured liquid, with a surface tension of less than 30 dynes/cm^2.

The composition is filled into suitable pressurized containers, and a suitable liquid aerosol propellant added so that the ratio of liquid propellant to composition is preferably in the

range of from 1 part by weight of propellant and 4 parts by weight of composition, to 1 part by weight of propellant to 14 parts by weight of composition more preferably a ratio of 1 part by weight of propellant to 9 parts by weight of composition. A preferred propellant for the above described composition is 1 part by weight of a 1.5 to 1.0 parts by weight mixture of dichlorodifluoromethane and dichlorotetrafluoromethane, although a 9.1 parts to 1 part mixture of isobutane and propane may also be used. The fill per container is preferably such that a vapour pressure of not more than 55 psig and not less than 35 psig at 70°F is obtained.

When the pressure is released, the formed foam extrudes at a uniform rate and has the following properties:

(a) *Micropore Size and Distribution*: The preferred pore-size for the formed foam is not less than 1 micron in diameter and not greater than 40 microns in diameter with a preferred range in micropore distribution of:

Pore Size (microns)	*% Range in Distribution*	*Found – % Distribution*
1 – 5	0 – 10%	8%
5 – 10	10 – 20%	14%
10 – 20	45 – 60%	53%
20 – 30	20 – 30%	22%
30 – 40	0 – 10%	3%

(b) *Foam Stability:* After one hour of atmospheric exposure the height of a two-inch foam column was unchanged but collapsed after 9 hours of standing. The calculated range for the half-life of the extruded foam is 5 to 7 hours.

(c) *Phase Reversal:* The phase reversal index for a 1 gm. sample of the formed foam is not more than 1% after 4 hours of covered exposure at room temperature as shown by separation, seepage and drainage.

To the above described formulation may be added suitable pharmaceutical aids such as buffering agent or silicone compounds, for example, dimethylpolysiloxane, methylpolysiloxane or phenyldimethylpolysiloxane.

When this foam is applied to burned, abraded and/or injured skin of humans or animals, there is virtually no pain experienced, in contrast to the severe pain and trauma caused by the use of the conventional degerming agents. Repeated daily applications of up to four times per day for extended periods of time, did not reveal any tendency to tissue sensitization and/or local irritation. Effective degerming of the skin and mucous membrane is rapidly achieved so that uneventful recovery results with minimal need for skin grafting.

When the above described germicidal foam was used to degerm the skin of a patient with 35% partial and full thickness burns of the face, forearms, hands and both legs, there was no pain on application of the germicidal foam and the patient was discharged after 10 days of treatment without any sign of topical infection or the need for skin grafting.

In the other study of burn patients, it was found that multiple application of the present foam resulted in rapid degerming of the skin so that there was no occurrence of topical infection during the treatment period, with uneventful healing. When the foam was used to cover abraded skin resulting after industrial injuries, a rapid pain-free degerming occurred without any evidence of topical infection during the treatment period. When the foam was used under a bandage there was no maceration of the skin as sometimes occurs when the conventional topical preparations are used and seal the skin.

The invention will now be illustrated by the following examples.

EXAMPLE 1

Preparation of a germicidal foam:

Step 1. 15 pounds of propylene glycol; 4.5 pounds of Poloxamer-188, which is marketed as Pluronic F-68 Wyandotte Chemicals Corporation of Michigan; 3 pounds of disodium phosphate; 2.2 pounds of citric acid anhydrous and 220 pounds of purified water were placed in a suitable container fitted with a stirrer and heating device. The mixture was stirred until complete solution was achieved and then 1 pound of Igepal-CO-630, which is marketed by General Aniline and Film Corporation, New York was added to the solution. The solution was heated to about 70°C and filtered.

Step 2. In a separate container, 3 pounds of cetyl alcohol were melted and 6 pounds of stearic acid dissolved in this melt with the aid of gentle heating. The temperature was maintained at about 65°C. to 70°C. and 0.3 pound of dimethylpolysiloxane was added to the melt of cetyl alcohol and stearic acid. The mix was stirred while the temperature was maintained at 65°C. to 70°C.

Step 3. The molten cetyl alcohol, stearic acid, silicone mixture obtained as a result of Step 2, were added to the solution obtained as a result of Step 1 and the mixture was stirred until a

homogenous dispersion resulted.

Step 4. When the dispersion had cooled to 30°c., 30 pounds of povidoneiodine powder were added and the mixture was stirred until the powder had completely dissolved. The pH was monitored continually so that it was never below pH 4.0 nor greater than pH 6.

Step 5. Sufficient purified water was added to bring the batch weight of 300 pounds and stirring was continued until the temperature was room temperature. The composition was allowed to stand overnight in a tightly-stoppered container. This product, known as the concentrate-dispersion, had a surface tension of between 25 and 28 dynes/cm^2 at 25°C. and a pH of 5.5.

Step 6. After suitable period of standing, the concentrate-dispersion was packaged in a pressurized container with a liquid aerosol propellant such as isobutane and/or propane or a halogenated hydrocarbon. The ratio of concentrate-dispersion to propellant was 9 parts by weight of concentrate-dispersion to 1 part by weight of liquid propellant. The interfacial tension between the concentrate and liquid propellant was between 0.5 and 1.5 dynes/cm^2 at 4.OC. When the liquid propellant-concentrate dispersion was filled into a pressurized container, the container pressure was not less than 35 psig and not greater than 55 psig at 70°F.

The pore size distribution of the formed foam was:

Pore Size (Microns)	*Percent Distribution*
0 – 5	7%
5 – 10	13%
10 – 20	51%
20 – 30	24%
30 – 40	5%

The height of a 2 inch foam column remained unchanged after one hours exposure to the atmosphere and collapsed after nine hours of standing. After four hours of standing under covered exposure at room temperature conditions, a 1 gm. aliquote foam sample showed no phase reversal.

EXAMPLE 2

10g of polyethyleneglycol-400; 15g of Igepal CO-630 and 150 of purified water were placed in a suitable container fitted with a stirrer and heating device. The mixture was stirred until complete solution was achieved and then warmed to about 70°C; a melt of 10 of lauryl alcohol and 20 g of linoleic acid was added, with vigorous stirring to achieve a uniform dispersion. The pH of the dispersion was adjusted to pH 5.5; cooled to room temperature and 5% by weight of silver sulfadiazine was added. The mixture was stirred to achieve a uniform distribution of the silver sulfadiazine and the whole allowed to stand overnight at room temperature. The surface tension of the concentrate was 24 dynes/cm^2 at 25°C. The concentrate dispersion was packaged in a pressurized container fitted with a release valve utilizing a mixture of 40% dichlorodifluoromethane and 60% dichlorotetrafluoroethane. The interfacial tension between the propellant and concentrate was 0.7 dynes. The range in container pressure was not less than 35 psig and not greater than 55 psig at 70°F. The micropore distribution of the formed foam was:

Pore Size (Microns)	*Percent Distribution*
0 – 5	5%
5 – 10	12%
10 – 20	54%
20 – 30	24%
30 – 40	4%

The pH of the formed foam was 5.5.

EXAMPLE 3

Stearyl alcohol, 0.5g and lauric acid 1.5g were mixed with 3g of glycerine and the whole warmed to 70°C. When solution was achieved, a solution of 1g of Pluronic F-68 dissolved in 45g of water was added and the mixture vigorously stirred, while the temperature was maintained at 70°C. The temperature was allowed to cool to room temperature and 3% by weight of erythromycin was added. The surface tension of the concentrate was 27 dynes/cm^2 at 25°C. The concentrate-dispersion was then packaged in a suitable pressurized container using a liquified fluorinated hydrocarbon, known as Freon (Registered Trade Mark) and marketed by Dupont Chemical Corp., as the propellant. The interfacial tension between the propellant and concentrate was 0.8 dynes. The resultant sprayable composition formed a

desirable foam that was useful in the treatment of burned, wounded and abraded skin and which had the following micro-pore distribution:

Pore Size (Microns)	*Percent Distribution*
0 – 5	7%
5 – 10	25%
10 – 20	49%
20 – 30	18%
30 – 40	1%

The pH of the formed foam was pH 3.2.

EXAMPLE 4

In place of the fatty alcohol described in Example 1 to 3 above, a saturated or unsaturated fatty alcohol such as decyl alcohol, dodecyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, stearyl alcohol, oleyl alcohol, linoleyl alcohol or a mixture thereof may be substituted in equal parts by weight. The ratio of the fatty alcohol to the fatty acids as used in Example 1 to 3 above and Example 5 below was 1:2, with a preferred range of from 0.5 to 1.5 parts by weight of fatty alcohol to 1:3 parts by weight of fatty acid. The remainder of the steps were the same and the formed foam was useful to degerm burned, abraded or injured skin and mucous membranes.

EXAMPLE 5

In place of the fatty acid described in Example 1 to 3 above, a fatty acid such as lauric acid, myristic acid, stearic acid, linolenic acid, linoleic acid, oleic acid or a mixture thereof may be substituted in equal parts by weight. The remainder of the steps were the same and the formed foam resulting was useful to degerm burned, abraded or injured skin and mucous membranes.

EXAMPLE 6

In place of the nonionic surface tension reducing agent described in Examples 1 to 5 above a poly(oxyethylene)-poly(oxypropylene)-polyethylene polyol compound, known in the trade as a Pluronic Polyol; an actylphenoxypoly-(etheneoxy)-ethanon compound, known in the trade as an Igepal CA compound; a fatty-acid-polyoxyalkyl ester of a hexahydric alcohol, known in the trade as a Span or Tween, or a mixture thereof may be substituted in equal parts by weight. The preferred concentration of the nonionic surface tension reducing agent must be at least equal in parts by weight to one-half of the combined weight of the fatty alcohol and fatty acid moieties but not greater than three times the weight of the fatty alcohol present. The remainder of the steps were the same and the formed foam was useful to degerm burned, abraded or injured skin and mucous membranes.

EXAMPLE 7

In place of the aliphatic glycol used in Examples 1 to 3 above, a liquid glycol compound such as polyoxyethylene glycol having a molecular weight of from 200 to 800, propylene glycol, glycerin or a mixture thereof may be substituted in equal parts by weight. The ratio of the selected glycol compound to the amount of water present in the finished formulation is 1 part by weight of selected glycol to 15 parts by weight of water with a preferred range of from 0.5 to 1.5 parts by weight of the selected glycol compound to 7.5 to 30 parts by weight of water. The remainder of the steps were the same and the resulting formed foam was useful to degerm burned, abraded or injured skin and mucous membranes.

EXAMPLE 8

In place of the dimethylpolysiloxane used in Example 1 above, another pharmaceutically acceptable silicone compound such as, methylpolysiloxane or phenyldimethylpolysiloxane may be substituted in equal parts by weight. The preferred range of concentration of the selected silicone compound was from 0.05% to 1.0% by weight.

The silicone compound described above may also be included in the foam formulations described in Examples 2 to 7 above, it is used in a preferred range in concentration of from 0.05% to 1.0% by weight.

EXAMPLE 9

In order to demonstrate the release of the active germicidal agent from the formed foam, trypticase soy agar plates were innoculated with a test microorganism, for example, stapylococcus aureus, ATCC6538; escherichia coli, ATCC 11229; proteus vulgaris, ATCC 13315; streptococcus fecalis, ATCC 8043; pseudomonas seruginosa, ATCC 104145; aerobacter aerogenes, ATCC 13048 or streptococcus pyogenes. Approximately 0.5 of the formed foam, for example the foam obtained as a result of Examples 1 to 7 above, was placed on the surface of each innoculated plate and the plates were then incubated at 37°C. for seven days and the zone in inhibition measured. Representative results of this test with the formed foam, obtained as a result of Examples 1, 2 and 3 above are:

TEST ORGANISM	*Zone of Inhibition of Microbicidal Growth with a foam, Obtained as a result of:* Example 1	Example 2	Example 3
Staphylococcus aureus, ATCC 6538	27mm.	19mm.	18mm.
Escherichia coli, ATCC 11229	26mm.	21mm.	16mm.
Proteus vulgaris, ATCC 13315	25mm.	20mm.	12mm.
Streptococcus fecalis, ATCC 8043	27mm.	21mm.	19mm.
Pseudomonas seruginosa, ATCC 104145	24mm.	22mm.	17mm.
Aerobacter aerogenes, ATCC 13048	28mm.	19mm.	14mm.
Streptococcus pyogenes	22mm.	19mm.	17mm.

EXAMPLE 10

In order to degerm burned skin of humans and animals, the foam formed as a result of Examples 1 to 8 above was applied to the injured tissue and/or mucous membranes from 1 to 6 times daily. A foam layer of at least one-half inch in height was applied to the injured area which could be covered or left uncovered, depending upon the particular patient's need. The film surface formed by the foam over the injured skin serves to provide a microbicidal barrier at the same time permitting gaseous interchange to avoid maceration. The treated burn sites healed rapidly, so that minimal skin grafting was required. A notable effect was the absence of pain during and after application of the germicidal foam to the injured area.

In a similar manner, abraded and wounded skin and mucous membranes could be degermed through the application of the germicidal foam from 1 to 6 times daily.

WHAT WE CLAIM IS:

1. A sprayable pharmaceutical composition for topical application to the injured skin of humans and animals comprising,

a) an aliphatic fatty alcohol of the formula ROH, in which R represents a saturated or unsaturated alkyl group of from 10 to 18 carbon atoms or a mixture thereof,

b) an aliphatic fatty acid of the formula RC00H which R represents a saturated or unsaturated alkyl group of from 14 to 18 carbon atoms or a mixture thereof, the concentration of the fatty acid being from 1 to 3 parts by weight of fatty acid for each part by weight of fatty alcohol,

c) a nonionic surface tension reducing agent which is a poly(oxyethylene)-poly(oxypropylene)-polyethylene polyol compound; an octylphenoxypoly-(ethyleneoxy)-ethanol compound or a fatty acid polyoxy-alkyl ester of a hexahydric alcohol or a mixture thereof, its concentration being at least equal to one-half of the combined weight of the fatty alcohol and fatty acid moieties, but not greater than three times the weight of the fatty alcohol present,

d) an aqueous-aliphatic glycol mixture, the glycol being a polyoxyethylene glycol, having a molecular weight of from 200 to 800; propylene glycol, glycerine or a mixture thereof in critical proportion of from 0.5 to 2.0 parts by weight of glycol to 7.5 to 30 parts by weight of water,

e) a therapeutically sufficient quantity of a microbicidal agent,

f) a suitable liquid aerosol propellant which is propane, isobutane, dichlorodifluoromethane, dichlorofluoromethane, chlorodifluoromethane, 1,1, 2 trichloro-1,2,2, trifluoroethane, dichlorotetrafluoroethane, carbon dioxide, nitrogen or a mixture thereof, in sufficient quantity to provide a ratio from 0.5 to 3 parts by weight of propellant to 7 to 9.5 parts by weight of sprayable composition, and, the whole being packaged in a suitable pressurized container fitted with a release valve, to permit the release of the formed foam for application to the injured skin.

2. A composition as claimed in claim 1 in which the ratio of liquid propellant to sprayable composition is 1 part by weight of propellant to 9 parts by weight of sprayable composition.

3. A composition as claimed in claim 1 or claim 2 in which the fatty alcohol is cetyl alcohol.

4. A composition as claimed in claim 1 or claim 2 in which the fatty alcohol is stearyl alcohol.

5. A composition as claimed in any of claims 1 to 4 in which the aliphatic acid is stearic acid.

6. A composition as claimed in any of claims 1 to 4 in which the aliphatic acid is palmitic acid.

7. A composition as claimed in any of claims 1 to 6 in which the nonionic surface tension reducing agent is nonylphenoxypoly(ethyleneoxy) ethanol.

8. A composition as claimed in any of claims 1 to 6 in which the nonionic surface tension reducing agent is a poly(oxypropylene)poly(oxyethylene) copolymer.

9. A composition as claimed in any of claims 1 to 8 in which the aliphatic glycol is propylene glycol.

10. A composition as claimed in any of claims 1 to 9 in which the microbicidally active agent is povidone-iodine.

11. A composition as claimed in any of claims 1 to 9 in which the microbicidally active agent is a nonylphenoxypolyethyleneoxyethanol iodine complex.

12. A composition as claimed in any of claims 1 to 9 in which the microbicidally active agent is silver sulfadiazine.

13. A composition as claimed in any of claims 1 to 9 in which the microbicidally active agent is silver sulfathiazine.

14. A composition as claimed in any of claims 1 to 9 in which the microbicidally active agent is sulfamylon.

15. A sprayable pharmaceutical composition as claimed in claim 1 substantially as herein described with reference to any of the Examples.

16. A method for preparing a composition as claimed in any of claims 1 to 15 comprising the steps of:

a) mixing from 0.5 to 1.5 parts by weight of the aliphatic glycol with from 7.5 to 30 parts by weight of water,

b) adding a nonionic surface tension reducing agent in a concentration at least equal to the combined weight of fatty alcohol and fatty acid moieties set forth in step c below,

c) melting one part by weight of the fatty alcohol and from two to three parts by weight of the fatty acid,

d) mixing the molten fatty alcohol-fatty acid mixture of step c with the aqueous-glycol solution obtained as a result of step b and stirring until a homogenous dispersion results,

e) adding a therapeutically sufficient quantity of the germicidal agent, and stirring until a homogenous dispersion results,

f) adding one part of the pharmaceutically acceptable liquid aerosol propellant to each nine parts of dispersion obtained as a result of step e and packing into a suitable pressurized container fitted with a release valve.

17. A method as claimed in claim 16 which further comprises the addition of a suitable pharmaceutically acceptable buffer to maintain the pH of the concentrate at between pH 4 and pH 6.

18. A method as claimed in claim 16 substantially as herein described with reference to any of the Examples.

19. A composition as claimed in claim 1 when prepared by a process as claimed in any of claims 16 to 18.

20. A method for degerming the surface of burned, abraded, injured or wounded skin and mucous membranes of non-human animals which comprises the application of the composition as claimed in any of claims 1 to 15 or claim 19 to the injured site.

21. The method for suppressing microbiologic growth on the surface of burned, abraded, injured or wounded skin and mucous membranes of non-human animals which comprises the application of the composition as claimed in any of claims 1 to 15 or claim 19 to the injured site.

22. A method for achieving a substantially pain-free release of a microbicidally active substance to degerm burned, abraded, wounded or injured skin and mucous membranes of non-human animals which comprises applying the composition as claimed in any of claims 1 to 15 or claim 19 to the injured site.

23. A method as claimed in any of claims 20 to 22 in which the composition is applied from 1 to 6 times daily to the injured site.

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